PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The contribution of primary prevention medication and dietary change in coronary mortality reduction in England between 2000 and 2007: a modelling study
AUTHORS	Guzman Castillo, Maria; Ahmed, Ridwaan; Hawkins, Nathaniel; Scholes, Shaun; Wilkinson, Ewan; Lucy, John; Capewell, Simon; O'Flaherty, Martin

VERSION 1 - REVIEW

REVIEWER	Chris Gale Univesrity of Leeds, UK
REVIEW RETURNED	07-Aug-2014

GENERAL COMMENTS	This population based primary prevention ecological study presents some interesting findings. There are a number of points, however, which require clarification. 1) Could I suggest that the authors condense the introduction to focus the argument for the investigation – placing some of the redundant text in the discussion? 2) Mention effect of hospital treatments – see: Resolving inequalities in care? Reduced mortality in the elderly after acute coronary syndromes. The Myocardial Ischaemia National Audit Project 2003-2010. Gale CP, Cattle BA, Woolston A, Baxter PD, West TH, Simms AD, Blaxill J, Greenwood DC, Fox KA, West RM. Eur Heart J. 2012 Mar;33(5):630-9. doi: 10.1093/eurheartj/ehr381. Epub 2011 Oct 18. PMID:22009446 3) The methods section concentrates predominantly on the modelling. Prior to this, the methods section should be expanded to include: a description of the data source, permissions, cleaning, coding, sampling frame, analytical cohort, along with a STROBE flow diagram. 4) please mention limitations due to unmeasured or non-modelled confounders / effect modifiers. Also the estimated of use of statins and HTN medication was derived from morbidity diagnoses rather than prescriptions data - what could be the effects of misclassification bias. Non-linear trends were not accounted for, 5) Explain how change in SBP and TC levels was calculated – did the authors adjust for regression to the mean, should they? 6) Give proportions of deaths as well as absolute numbers of

	estimated DPPs – numbers sometimes seem a bit alarmist 7) Did the authors adjust for a change in life expectancy over time? I know that this is a circler argument, but life expectancy could have increased due to other nonCV factors, at a different rate over time. Presumably the model assumes that treatment / and or life style factors have an immediate (1 year time allocated) latency effect, when in fact such interventions are likely to have a much longer lag effect. Please explain. Can the team account for this in their analyses – or is it an assumption (which also does not change of the study period?).

REVIEWER	Tony Blakely University of Otago, Wellington
REVIEW RETURNED	10-Sep-2014

GENERAL COMMENTS	Re statistics, in my revie I propose that a more specific measure of difference in % due to (say) BP between sex should be included. This would lift paper. This paper is a useful contribution, to both the contribution of population-wide versus high risk treatment, and the playing out for inequalities. I have only moderate to minor comments. The presentation of mutually exclusive DPPs in the abstract, whilst perhaps easier for communication, is prresumably wrong. If statins only were instituted, they would prevent some of the DPPs that population wide measure would prevent. Perhaps it might pay to state in the Abstract that a 'mutually exclusive assignation of cause method was used'? In the conclusion of the Abstract, should it not say?: "Mortality reductions were greatest in <u>absolute terms in</u> the most deprived quintiles …" (I also believe that the absolute versus relative impact on inequalities could be teased out a little better in the Discussion.) The statement: "Future CHD prevention strategies should prioritise healthy diet policies ahead of medications" is not justified (within what we see in abstract anyway). The fact that population preventions were the biggest cause in the recent decade does not mean: - It will therefore be so in the next decade (although maybe it could be argued) - That this is where policy can have the biggest influence – policy influences further shifts over and above business as usual. Maybe future reductions are 'locked in' already due to recent and inevitable trends in risk factors regardless of policy does. - Finally, cost effectiveness of interventions that will do more than BAU (or what is already locked in) should ideally be considered.

	I may sound a bit pedantic here. But I believe the point is important. And indeed it is one levelled at the GBD. Just because the biggest burden is due to X, and YY% of X is due to risk factor Z, it does not (necessarily) follow that the policy priority should be on Z. This statement requires knowing how much more gain (over and above BAU) can be gained by actual interventions acting on Z, and at what cost effectiveness, and compared to other hypothetical interventions actin on Z or other risk factors/treatments. I would be less apologetic about using area-level deprivation. Socioeconomic position is a multi-dimensional construct. A measure of income in the last year (even if well done) is not going to be a perfect measure of lifetime income, let alone assets, education, class, etc. No measure is. Area-level deprivation has advantages, representing the destination of accumulated socioeconomic position, preference, etc. Put another way, any single socio economic factor measure will suffer from measurement error when held up against the 'true' construct of individual-level socioeconomic position. Small area deprivation is no different in this regard, and may even have strengths. "Observed differences in CHD mortality might reflect not material deprivation but other confounding factors such as alcohol consumption, obesity or ethnicity." Aren't these more likely to be mediating factors between socioeconomic position and CHD? Therefore, adjusting for them overadjusts (i.e. generating an estimate of the direct effect). "The UK has experienced a remarkable 60% reduction in coronary heart disease (CHD) mortality since the 1970s." Actually, all 'rich' countries have, and by as much as 80%. See mortalitytrends.org (i.e. the late Gary Whitlock's site). Table 1 does not appear to be referenced in the main text. Are the differences in risk factor and treatment contributions by sex (Figure 4) overplayed? I think so. The biggest uncertainty will be the change in risk factor distribution over time (with uncertainty as Table B inputs). There is uncertainty about the DPPS in the Appendix (Table C onwards). There is no uncertainty given about a metric that directly 'tests' the hypothesis that (say) BP contributed to greatest reductions in females. In my view, there should be. More exactly, if the hypothesis is: "does BP make a bigger percentage reduction among females" … then the IMPACT model, using Ersatz, can be configured to do this. (I note in passing, however, that if you have set up Ersatz to run two loops (i.e. 'multiple runs' option checked, thus meaning that there are iterations looped within runs), it is tricky to get this output out using Erpercentile and other functions directly on the cells in Excel. Rather one has to extract the internal output within Erzatz to a sheet and extract information thence. But it can be done.) One would then construct (say) a metric for 'difference in percent reduction by X between males and females' with uncertainty. I think this would greatly improve the quality of the outputs of the modelling at the moment. (Is uncertainty in both 2000 and 2007 risk factors estimates included in estimation, and propagated through to uncertainty in BP impact?

	Correlations of 2000 and 2007 estimate may be important, but probably unknown, so best set at 0 in main analyses with sensitivity analyses of ? 0.25.) In previous referee reports on IMPACT studies, I have queried why they do not model (health/quality of) life years saved. It would be better. DPPs might be a one day or a one decade postponement of an incident case, or enough postponement for another competing disease to 'claim' the subject. We simply do not know. Moreover, when looking at socio-economic inequalities there is the vexed issue of higher background morbidity and mortality among the lower socioeconomic group, meaning that the actual health gain per DPP will be less [1] – resulting in a lesser reduction in inequalities than a DPP alone would suggest. However, for this paper I think DPP is sufficient, so long as this issue of lesser health gains (in health/quality adjusted life years) is mentioned in the discussion. Minor Page 29 (i.e. Appendix). Line 11. Replace row with column. 1. McLeod M, Blakely T, Kvizhinadze G, Harris R. Why equal treatment is not always equitable: The impact of existing ethnic health inequalities in cost effectiveness modelling. *Popul Health Metrics* 2014; **12**(15).

VERSION 1 – AUTHOR RESPONSE

Reviewer Chris Gale

1. Could I suggest that the authors condense the introduction to focus the argument for the investigation placing some of the redundant text in the discussion?

Many thanks for your comment. The introduction has been pruned, and now reads:

The UK, as many other industrialised countries, has experienced a remarkable 60% reduction in coronary heart disease (CHD) mortality since the 1970s. However CHD remains the leading cause of premature death (3).

Approximately one third of this initial CHD mortality reduction was attributable to treatments, and two thirds to reductions in major risk factors. The biggest contributions came from a large decline in smoking prevalence since the 1960s, and more recent reductions in blood pressure and cholesterol (1, 4).

The CHD mortality declines have demonstrated a changing relationship with socio-economic status (SES) (5-7). Initially, it demonstrated a positive relationship with SES (i.e.
with affluence) (8). However, this has now reversed in more recent studies in the UK, US, New Zealand, Australia, and Scandinavia (9-11)

Risk factors have also demonstrated strong socioeconomic patterning. Substantial positive associations between lower SES and higher smoking prevalence and higher blood pressure levels have been reported in several studies (12-14). However, for cholesterol, the evidence has been less dramatic, with a higher intake of saturated fats among the more deprived populations reported in most studies (15-17), but not all (18-20). Socioeconomic differences in both risk factors may thus explain some of the CHD mortality gradients. Thus, any attempt to reduce the CHD burden and tackle the associated socioeconomic inequalities should explicitly consider these major risk factors (21).

Primary prevention medications to lower blood pressure and cholesterol have therefore been standard UK health policy for almost two decades. However, while their quantitative benefits to whole

populations are accepted, their potential contributions to reduce inequalities are less clear (7,9,21,28,29,35,36).
The aim of this study was therefore to analyse the recent falls in CHD mortality and quantify the relative contributions from preventive medications and from population-wide
changes in blood pressure and cholesterol levels, particularly exploring the potential effects on socioeconomic inequalities.
2. Mention effect of hospital treatments – see: Resolving inequalities in care? Reduced mortality in the elderly after acute coronary syndromes. The Myocardial Ischaemia National Audit Project 2003-2010.Gale CP, Cattle BA, Woolston A, Baxter PD, West TH, Simms AD, Blaxill J, Greenwood DC, Fox KA, West RM.Eur Heart J. 2012 Mar;33(5):630-9. doi: 10.1093/eurheartj/ehr381. Epub 2011 Oct 18. PMID:22009446
Thank you for the reference. We definitely agree that treatments have contributed significantly to CHD mortality reduction in the last decades. In fact, the results of Gale et al (2012) support the findings of a study conducted by Bajekal et al (2011) using our IMPACTSEC model where approximately 12,700 deaths were postponed or prevented (33% mortality reduction) in England during 2000 and 2007 due to other type of treatments such as the ones mentioned in the reference above plus treatments for secondary prevention post myocardial infarction, secondary prevention post revascularisation, chronic stable coronary artery disease, heart failure patients admitted to hospital and heart failure patients resident in the community.
We decide to focus our paper in primary prevention only, however we mentioned in the results section that other treatments and change in risk factors contributed to a 32% of the mortality reduction. Nevertheless we have included the reference as you suggested.
3. The Methods section concentrates predominantly on the modelling. Prior to this, the methods section should be expanded to include: a description of the data source, permissions, cleaning, coding, sampling frame, analytical cohort, along with a STROBE flow diagram.
Many thanks for your comments. We agree that definitely a good description of the data sources and processing is needed. However, given the wide variety and amount of data used to build the model, we do not think is terribly easy to persuade editors to include all the very extensive details in the main manuscript. Instead we have enhanced the technical appendix to include a very detailed description. We also have included the appropriate links on the methods section.
4. Please mention limitations due to unmeasured or non-modelled confounders / effect modifiers. Also the estimated of use of statins and HTN medication was derived from morbidity diagnoses rather than prescriptions data- what could be the effects of misclassification bias. Non-linear trends were not accounted for,
Many thanks. We have added a paragraph to the limitations section. Now it reads:
Our risk factor effect data might still have some residual confounding. Statins and anti-hypertensive medication data is from surveys, therefore some misclassification bias might be present.
5. Explain how change in SBP and TC levels was calculated – did the authors adjust for regression to the mean, should they?
Thanks, we have included in the appendix how we derived SBP and cholesterol levels. Now it reads:
The annual sample size of the Health Survey for England (HSE), roughly 14,000 adults aged 16 years and over, was not large enough to provide accurate and precise estimates of risk factor levels, and hence rates of change over time by age, sex, and deprivation quintiles. We considered a ‘fixed gradient approach’ for estimating risk factors changes.
The fixed gradient approach is based on the assumption that changes in pace and direction for each deprivation quintile were similar and therefore, most accurately measured by the overall national rates of change (across all age-sex groups). If this assumption holds, then relatively stable and plausible estimates for each quintile could be derived by scaling the national age-sex risk factor levels up or down using a fixed ratio/gradient.
The fixed gradient was derived by pooling together survey data for all available years from 2000 to 2007 to calculate risk factor estimates by age, sex, and deprivation quintiles. Then the pooled national estimate for 14 age-by-sex groups was set notionally to one, and the corresponding estimates for

each deprivation quintile re-indexed to be below or above one (i.e. expressing the ratio of the deprivation quintile to national estimate). These index rates were then applied to the single year national estimates to derive the corresponding risk factor levels for that year. The fixed gradient was applied to both the start and end years of the model. The next table shows the risk factor levels in 2000 and 2007 by gender and deprivation quintiles using this approach.

6. Give proportions of deaths as well as absolute numbers of estimated DPPs – numbers sometimes seem a bit alarmist
Thank you. We have modified the manuscript accordingly to include percentages of mortality reduction for the main outcomes.
7. Did the authors adjust for a change in life expectancy over time? I know that this is a circler argument, but life expectancy could have increased due to other nonCV factors, at a different rate over time.
Many thanks. We did not adjust for changes in life expectancy. In our model, we compare the number of observed deaths in 2007 with the expected number of deaths in 2007 had mortality rates from 2000 (and therefore life-expectancy) remained unchanged

8. Presumably the model assumes that treatment / and or life style factors have an immediate (1 year time allocated) latency effect, when in fact such interventions are likely to have a much longer lag effect. Please explain. Can the team account for this in their analyses – or is it an assumption (which also does not change of the study period?).
Many thanks for your comment. We have included this as a limitation.
However, we have highlighted the evidence suggesting that lag times for CHD mortality are probably short and that significant effects for both type of treatments have been observed early on in RCT. The limitations section now includes:
We assumed that treatments and lifestyle changes have an immediate effect on CHD mortality, which might not be entirely true. However, Capewell and O'Flaherty (29, 30) pointed out evidence from clinical trials and policy interventions which consistently suggests that changes in diet and lifestyle across entire populations can be rapidly followed by dramatic declines in mortality.
Reviewer Tony Blakely
1. Re statistics, in my review I propose that a more specific measure of difference in % due to (say) BP between sex should be included. This would lift paper.
Many thanks. We believe your point goes along with the point number ten, below.

2. The presentation of mutually exclusive DPPs in the abstract, whilst perhaps easier for communication, is presumably wrong. If statins only were instituted, they would prevent some of the DPPs that population wide measure would prevent. Perhaps it might pay to state in the Abstract that a 'mutually exclusive assignation of cause method was used'?
Many thanks for your valuable comment. As we mentioned in the methods section, we considered that some overlap between pharmacological and non-pharmacological contributions to risk factor DPPs might occur. Therefore, to estimate the impact of population-wide reduction in total cholesterol due to non-pharmacological change only, we subtracted the estimated effect of cholesterol-lowering treatments uptakes levels change from the overall number of DPPs due to change in mean total cholesterol. A similar procedure was carried out for SBP and anti-hypertension treatments.
We have now edited the limitations section to better reflect your suggestion: "We simply subtracted the mortality gains from increasing uptake levels of statins from the overall gains due to reductions in total cholesterol to estimate the impact of population-wide reduction in total cholesterol due to non-pharmacological change only. This mutually exclusive adjudication of cause adjustment might overestimate medication benefit"

3. In the conclusion of the Abstract, should it not say?:"Mortality reductions were greatest in absolute terms in the most deprived quintiles …"

Thanks for this helpful suggestion. We have modified the sentence as you suggested.

4. (I also believe that the absolute versus relative impact on inequalities could be teased out a little better in the Discussion.)
Many thanks. We have now mentioned in the manuscript there is not a statistical significant SES gradient in the number of deaths prevented or postponed. Therefore the relative impact on equalities for each IMDQ was no different from that observed in England.
The section on SBP in page 11 now reads:
… Conversely, changes in treatment uptake levels demonstrated the opposite effect, since more deaths were prevented in the most affluent quintile compared to the most deprived. However in both cases, SES differences were not statistically significant..
The section on cholesterol in page 11 now reads:
… Conversely, population changes in cholesterol resulted in approximately 700 (500-1,000) DPPs in the most deprived quintile and some 200 (40-400) DPPs in the most affluent quintile. However, like SBP there was no a clear SES gradient.
5. The statement: “Future CHD prevention strategies should prioritise healthy diet policies ahead of medications” is not justified (within what we see in abstract anyway). The fact that population preventions were the biggest cause in the recent decade does not mean:
- It will therefore be so in the next decade (although maybe it could be argued)
- That this is where policy can have the biggest influence – policy influences further shifts over and above business as usual. Maybe future reductions are ‘locked in’ already due to recent and inevitable trends in risk factors regardless of policy does.
- Finally, cost effectiveness of interventions that will do more than BAU (or what is already locked in) should ideally be considered.
I may sound a bit pedantic here. But I believe the point is important. And indeed it is one levelled at the GBD. Just because the biggest burden is due to X, and YY% of X is due to risk factor Z, it does not (necessarily) follow that the policy priority should be on Z. This statement requires knowing how much more gain (over and above BAU) can be gained by actual interventions acting on Z, and at what cost effectiveness, and compared to other hypothetical interventions actin on Z or other risk factors/treatments.
Many thanks for your helpful and shrewd comments. We agree that simply because population preventions were the biggest cause of mortality reduction, we should not focus only on this type of interventions. As we mentioned in the conclusion:
“There is no simple choice between either population-based or high risk strategies to reduce CHD mortality. The approaches are complementary in delivering the greatest public health benefit (39, 40). It is, however, clear that individual-based treatment strategies can afford only modest reductions in mortality compared with addressing risk factors population wide.
Severely limited health care budgets are now forcing planning systems to consider how best to allocate future resources. Our results strengthen the case for greater emphasis on preventive approaches, particularly population based policies to reduce blood pressure and cholesterol. Such strategies might be more powerful, rapid, cost-effective, and equitable than additional preventive medications (36)”
We have modified the conclusion in the abstract to reflect these ideas. Now it reads:
Population-wide secular changes in blood pressure and cholesterol levels helped to substantially reduce CHD mortality and the associated socioeconomic disparities. Mortality reductions were greatest in the most deprived quintiles, mainly reflecting their bigger initial burden of disease. Statins for high-risk individuals also made an important contribution but maintained socioeconomic inequalities.
Our results strengthen the case for greater emphasis on preventive approaches, particularly population based policies to reduce blood pressure and cholesterol

6. I would be less apologetic about using area-level deprivation. Socioeconomic position is a multi-

dimensional construct. A measure of income in the last year (even if well done) is not going to be a perfect measure of lifetime income, let alone assets, education, class, etc. No measure is. Area-level deprivation has advantages, representing the destination of accumulated socioeconomic position, preference, etc. Put another way, any single socio economic factor measure will suffer from measurement error when held up against the 'true' construct of individual-level socioeconomic position. Small area deprivation is no different in this regard, and may even have strengths.
Many thanks for your words. We have modified the paragraph to add a more positive view on the IMD. Now it reads:
Firstly, the area-level categorisation may not be representative of individual circumstances. Furthermore, observed differences in CHD mortality might reflect not material deprivation but other confounding and mediator factors such as alcohol consumption, obesity or ethnicity. However, the IMD is a comprehensible multi-dimensional construct of socioeconomic status made up of seven domains, and based on small geographical areas (less than 1500 residents) called Lower Level Super Output Areas (LSOAs). The advantage of using LSOAs is that their smaller geographical sizes also allow for a more detailed knowledge of deprived areas.
7. "Observed differences in CHD mortality might reflect not material deprivation but other confounding factors such as alcohol consumption, obesity or ethnicity." Aren't these more likely to be mediating factors between socioeconomic position and CHD? Therefore, adjusting for them overadjusts (i.e. generating an estimate of the direct effect).
Many thanks for your comment. You are correct and we have modified the sentences to avoid potential misunderstanding. Now it reads:
Furthermore, observed differences in CHD mortality might reflect not material deprivation but other confounding and mediator factors such as alcohol consumption, obesity or ethnicity.
8. "The UK has experienced a remarkable 60% reduction in coronary heart disease (CHD) mortality since the 1970s." Actually, all 'rich' countries have, and by as much as 80%. See mortalitytrends.org (i.e. the late Gary Whitlock's site).
Thanks. You are correct, most of the industrialised countries have experimented significant reduction in CHD mortality since 1970's. We have modified our introduction and it now reads:
The UK, as many other industrialised countries, has experienced a remarkable 60% reduction in coronary heart disease (CHD) mortality since the 1970s.
9. Table 1 does not appear to be referenced in the main text.
Thanks for noticing this error. It has now been corrected.
10. Are the differences in risk factor and treatment contributions by sex (Figure 4) overplayed? I think so. The biggest uncertainty will be the change in risk factor distribution over time (with uncertainty as Table B inputs). There is uncertainty about the DPPS in the Appendix (Table C onwards). There is no uncertainty given about a metric that directly 'tests' the hypothesis that (say) BP contributed to greatest reductions in females. In my view, there should be. More exactly, if the hypothesis is: Does BP make a bigger percentage reduction among females" then the IMPACT model, using Ersatz, can be configured to do this. (I note in passing, however, that if you have set up Ersatz to run two loops (i.e. 'multiple runs' option checked, thus meaning that there are iterations looped within runs), it is tricky to get this output out using Erpercentile and other functions directly on the cells in Excel. Rather one has to extract the internal output within Erzatz to a sheet and extract information thence. But it can be done.) One would then construct (say) a metric for 'difference in percent reduction by X between males and females' with uncertainty. I think this would greatly improve the quality of the outputs of the modelling at the moment.
Many thanks. You are correct; the results of the uncertainty analysis suggest that although there is a sex difference, this is not statistically significant. As you suggested we configured our model along with Ersartz to compute the relative difference between men and women for all the major outputs. The results (not included here) indicated that there are no significant differences between men and women, except for cholesterol: the number of deaths prevented or postponed due to population wide changes in cholesterol were four times higher in men than in women.
We have rewritten this section in the manuscript to convey the appropriate message. Now it reads:

Gender differences

Figures 4 shows the number of deaths prevented or postponed in men and women, from falls in the population mean levels of SBP and cholesterol (Figure 4a, left panels) and from increases in the treatment uptakes levels (Figure 4b, right panels). For men, although most of the mortality reduction came from population falls in SBP, cholesterol reductions have also a considerable larger effect in reducing mortality compared to women (four times higher). By contrast, the number of DPPs due to increases in treatment uptake in men appeared remarkably equitable across SES groups.

For women, the impressive reduction in SBP mean level between 2000 and 2007, contributed the most to the total mortality reduction and in all quintiles, whereas population level reductions of cholesterol had a smaller benefit. Moreover, the joint benefit of increasing treatment uptakes (antihypertensive and statins) in women appeared to have an important effect: for example, in the most affluent quintile (IMDQ1) the reduction in DPPs due to the increase in uptakes for women was almost as effective as the population-wide falls in both sexes for that quintile.

However, in terms of differences between men and women, the results of the uncertainty analysis suggest that these are not significant in statistical terms. More detailed outputs split by gender can be found in the section 5 of Technical Appendix.

11. (Is uncertainty in both 2000 and 2007 risk factors estimates included in estimation, and propagated through to uncertainty in BP impact? Correlations of 2000 and 2007 estimate may be important, but probably unknown, so best set at 0 in main analyses with sensitivity analyses of 0.25.)

Thanks, we included uncertainty in the mean values of SBP and Cholesterol assuming a normal distribution with mean and standard deviation extracted from the HSE. However we have not taken into account correlation between the two points in time. But as you indicate this may be very small.

12. In previous referee reports on IMPACT studies, I have queried why they do not model (health/quality of) life years saved. It would be better. DPPs might be a one day or a one decade postponement of an incident case, or enough postponement for another competing disease to 'claim' the subject. We simply do not know. Moreover, when looking at socio-economic inequalities there is the vexed issue of higher background morbidity and mortality among the lower socioeconomic group, meaning that the actual health gain per DPP will be less 1 – resulting in a lesser reduction in inequalities than a DPP alone would suggest. However, for this paper I think DPP is sufficient, so long as this issue of lesser health gains (in health/quality adjusted life years) is mentioned in the discussion.

Many thanks for your suggestions. We will take them in consideration for future research and added the idea to the discussion section:

Given the background of higher mortality and morbidity in the more deprived quintiles, DPPs might overestimate the actual health gain, as we don't know the additional life span gained by preventing a specific death at a specific time. This might result in a lesser reduction in inequalities than a DPP alone would suggest.

13. Page 29 (i.e. Appendix). Line 11. Replace row with column.

Many thanks for pointing out this; it has been now been corrected.

VERSION 2 – REVIEW

REVIEWER	Chris Gale University of Leeds
REVIEW RETURNED	04-Nov-2014

GENERAL COMMENTS	I am happy that the authors have addressed my comments.

REVIEWER	Tony Blakely University of Otago, Wellington, NZ
REVIEW RETURNED	29-Oct-2014

GENERAL COMMENTS	The authors have satisfactorily responded to my suggestions.